Follow-up to NAS meeting:

Question: What criteria did EPA use to evaluate the overall WOE for noncancer health effects of formaldehyde? Where in the document is this given?

Reply:

EPA's draft assessment analyzed the available formaldehyde database and then proceeded with successive steps aimed at winnowing down the studies used and synthesizing the data. First, the assessment examined individual studies and critically evaluated study quality. Second, EPA evaluated the entire set of studies relative to each type of endpoint, and made a weight of evidence judgment as to whether formaldehyde exposure is associated with a given effect. Third, for those endpoints that EPA judged to be associated with formaldehyde exposure, EPA then examined the studies to identify which had adequate data for making quantitative estimates for points of departure and which of those were the most appropriate studies to use for derivation of an RfC with respect to that endpoint, which it referred to as "candidate RfCs." Finally, because an RfC is intended to be "…without an appreciable risk of adverse health effects…," EPA selected the endpoints and candidate RfCs that were protective of all of the significant adverse effects, though in this case the draft recommended averaging across some very closely-related candidate RfCs.

Because EPA has articulated recommendations for many of these steps in general guidance documents or reviews, EPA's draft formaldehyde assessment does not include a section articulating the criteria for all of the above steps. Instead, it cites existing EPA guidances and reviews.

The following response provides references to EPA guidance and reviews that articulate the criteria EPA uses for evaluating the weight of evidence for noncancer endpoints and for developing an RfC. It also identifies those parts of the formaldehyde draft assessment that apply those criteria to the formaldehyde data or expand upon the general criteria.

EPA Guidance on criteria for noncancer risk assessment:

EPA has recommendations for the types of evidence to consider and how to evaluate the available evidence in a WOE evaluation for determining if noncancer health effects are agent-related. These recommendations can be found in the following EPA documents:

U.S. EPA. (1991) Guidelines for developmental toxicity risk assessment. Federal Register 56(234):63798-63826. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington, DC; EPA/600/8-90/066F. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (1996) Guidelines for reproductive toxicity risk assessment. Federal Register 61(212):56274-56322. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (1998) Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926-26954. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA. (2002) A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC; EPA/630/P-02/0002F. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

In general, the Agency derives a reference value (RfV) (e.g. reference concentration, RfC, or reference dose, RfD) if the effect has biological significance and there is adequate exposure-response information to support RfV derivation. The RfV is generally based on a critical effect defined as the first adverse effect, or its known precursor, that occurs in the most sensitive species as the dose rate of an agent increases.

The 2002 review of the RfC and RfD processes describes: 1) specific criteria for reviewing the adequacy and strength of studies 2) criteria to evaluate the applicability of animal studies to human health risk 3) characterization of susceptible populations and 4) evaluating the adequacy of the overall database (EPA, 2002){See attached excerpt}.

In addition, as referenced above, EPA has some guidelines for specific types of noncancer effects. For example, the EPA guidelines for neurotoxicity, reproductive toxicity, and developmental toxicity risk assessment discuss which types of outcomes are considered adverse and provide guidance on when the available evidence may be considered “sufficient” in defining the minimum evidence necessary to characterize the hazard and conduct a dose-response analysis (EPA, 1998; EPA 1996; EPA 1991). Finally, the EPA RfC methods document includes an appendix which presents criteria to define adverse respiratory health effects observed in epidemiologic studies (EPA 1994).

Discussion in the formaldehyde Assessment:

All of the above EPA guidelines informed the characterization of the overall WOE for noncancer health effects in Section 4.4 for each health effects category, although the criteria are not restated but instead are included by reference in the formaldehyde assessment.

Section 5.1.1 considers each of these health effects categories again; reviewing the WOE for each formaldehyde- related health effect and then evaluating if the available data can support RfC derivation. For this discussion, the criteria are discussed in general

terms in the introduction (Section 5.1.1). These discussions are consistent with, but don't expand upon, EPA guidance.

As there were many studies which would have met EPA's minimum criteria for establishing a formaldehyde-related health effect and providing a basis for the RfC (Section 5.1.1), EPA employed an additional screening process to identify the most appropriate studies for RfC derivation. Section 5.1.2.1 provides these criteria and an evaluation to focus RfC derivation on the most appropriate studies. These criteria are consistent with EPA guidance as described in EPA (2002) (e.g. preference for human data where available) and include factors that evaluate the study strength and confidence in the data (e.g. size/statistical strength, and quality of exposure characterization).